Biol Blood Marrow Transplant 19 (2013) 1288–1300

Reviews

Monoclonal Antibodies in Conditioning Regimens for Hematopoietic Cell Transplantation

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Article history:
Received 3 March 2013
Accepted 16 April 2013

Key Words:
Monoclonal antibody
Autologous
ematopoietic cell transplantation
Allogeneic hematopoietic cell transplantation

A B S T R A C T

Monoclonal antibodies are increasingly being incorporated in conditioning regimens for autologous or allogeneic hematopoietic cell transplantation (HCT). The benefit of adding rituximab to autologous HCT regimens is purportedly related to *in vivo* purging of clonal B cells. Randomized trials comparing the addition (or not) of rituximab to high-dose therapy regimens are lacking. No benefit of standard-dose radioimmunotherapy-based regimens for autografting in aggressive lymphomas was seen in a randomized controlled study. The incorporation of rituximab into allogeneic HCT regimens aims to improve responses while reducing nonrelapse mortality resulting from acute graft-versus-host disease. The optimal dose and administration schedule of rituximab in this setting are unknown, and potentially serious complications from increased infections owing to prolonged (and profound) cytopenias or persistent hypogammaglobulinemia are of concern. Radioimmunotherapy-based conditioning for allografting holds promise as a modality to optimize tumor control and synergize adoptive immunotherapy effects, but it remains experimental at this time. The addition of alemtuzumab to allogeneic HCT regimens is associated with prolonged lymphopenia and impaired immune reconstitution, high relapse rates, and serious infections. The optimal dose and schedule of alemtuzumab to avoid prolonged immune paresis remain elusive. It is anticipated that additional monoclonal antibodies will soon become available that can be incorporated into HCT regimens after safety and clinical efficacy are demonstrated.

INTRODUCTION

The past decades witnessed significant advances in development of monoclonal antibodies (mAbs) for treatment of various neoplasms [1-3]. The use of mAbs, either as monotherapy or in combination with conventional chemotherapies, has become the standard of care for various diseases [4]. These agents are also being incorporated into conditioning regimens for autologous (auto) and allogeneic (allo) hematopoietic cell transplantation (HCT). For high-dose therapy (HDT) and auto-HCT, the main benefits of adding mAbs are further improved efficacy, reduced relapse, and ultimately improved cure rates. Although these are also major reasons for using mAbs in the allo-HCT setting, other benefits, including reducing the incidence and severity of graft-versus-host disease (GVHD), are seen as well [5]. mAbs—namely, rituximab and alemtuzumab—also induce responses in corticosteroid-refractory GVHD [6-8]; however, this effect is not the focus of the present review. Here, we review the published literature pertaining to the use of mAbs in HCT conditioning regimens.

RITUXIMAB

Rituximab, a chimeric anti-CD20 mAb, is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of various subtypes of B cell non-Hodgkin lymphoma (NHL). Rituximab exerts its function via complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. According to the literature, combining rituximab with HDT is feasible and results in improved outcomes.

Rituximab in Conditioning Regimens for Autografting

HDT followed by auto-HCT is the standard of care for chemosensitive, relapsed aggressive NHL [9]. Historically, total body irradiation (TBI) was combined with cyclophosphamide or other agents as conditioning before autografting [9]. However, transplantation centers worldwide have moved away from TBI-based to chemotherapy-based regimens, because in part to the increased risk of subsequent myelodysplastic syndrome (MDS) and/or secondary acute myelogenous leukemia (AML) [10]. Commonly used auto-HCT regimens for NHL or Hodgkin lymphoma include combination therapy with carmustine, etoposide, cytarabine, and melphalan (BEAM); cyclophosphamide, carmustine, and etoposide; busulfan and cyclophosphamide; carmustine, etoposide, cytarabine and cyclophosphamide; and busulfan plus melphalan [9,11-19]. The choice of regimen depends on center preference and physician experience.

Financial disclosure: See Acknowledgments on page 1297.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.04.016

Rituximab is an essential component of front-line or more advanced therapy, as maintenance, and in conjunction with HCT regimens [20-24]. Randomized controlled studies (RCTs) demonstrating the superiority of rituximab in auto-HCT are lacking. Flohr et al. [25] combined rituximab with dexamethasone-BEAM as a mobilization therapy in 27 patients with B cell NHL and found profound peripheral B cell depletion without engraftment delay [25]. In that study, rituximab was also administered on days -10 and -3 of conditioning and was associated with an overall survival (OS) of 95% and a progression-free survival (PFS) of 77% at 16 months, respectively [25]. Khouri et al. [26] administered premobilization rituximab (375 mg/m^2 at 1 day before and 1000 mg/m^2 at 7 days after chemotherapy) and high-dose rituximab 1000 mg/m^2 on days +1 and +8 with BEAM before auto-HCT in 67 patients with *de novo* diffuse large B cell lymphoma (DLBCL) or aggressive lymphoma with a follicular component and reported 2-year disease-free survival of 67% and OS of 87%. A retrospective multicenter analysis of HDT and auto-HCT, with or without rituximab, in patients with DLBCL and follicular NHL showed that adding rituximab improved OS ($P < .001$) and event-free survival ($P < .001$) [27]. In a phase 2 study, Hicks et al. [28] administered rituximab at the time of stem cell collection, as an *in vivo* purging strategy and as posttransplantation maintenance in patients with follicular NHL, resulting in durable molecular remissions.

Potential concerns with rituximab use include the risk of opportunistic infections, such as cytomegalovirus (CMV), prolonged hypogammaglobulinemia, transient cytopenias, and delayed platelet engraftment [20,23,25,26,29]. The Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) conducted a randomized phase 3 trial comparing BEAM plus rituximab and ^{131}iodine-tositumomab (^{131}I-T)-BEAM conditioning for auto-HCT in patients with relapsed DLBCL (n = 224) [30]. Rituximab 375 mg/m^2 was given with BEAM on days -19 and -12. Rituximab-BEAM was accepted as the comparator arm in this trial. At a median follow-up of 25.5 months, rituximab-BEAM was associated with a 2-year PFS of 48.6%. Neutrophil engraftment was achieved by day +28 in 93.5% of the patients. The comparison with ^{131}iodine-tositumomab-BEAM is discussed in the information to follow. Selected studies using rituximab in auto-HCT are summarized in Table 1. Some centers have adopted a rituximab-BEAM regimen as the standard for auto-HCT in patients with B cell NHL; however, convincing RCT-based evidence demonstrating the superiority of rituximab in auto-HCT remains lacking.

Rituximab in Allo-HCT Conditioning Regimens

As the benefits of adoptive immunotherapy mediated by donor T cells became clearer, practice shifted toward reducing the intensity (and toxicity) of conditioning regimens for allo-HCT. Accordingly, allo-HCT using reduced-intensity conditioning (RIC) is now offered to patients of advanced age or with associated comorbidities who would not have been otherwise eligible for this procedure previously [31,32]. The development of RIC regimens occurred around the time when targeted therapies were being introduced into practice; thus, combining these approaches in an attempt to improve outcomes was a logical approach to pursue. Lower nonrelapse mortality (NRM) has been associated with the addition of rituximab to RIC regimens, but these data are not based on RCTs.

In 2001, Khouri et al. [5] reported encouraging results with the addition of rituximab to a RIC regimen of fludarabine and cyclophosphamide. In a cohort of 20 patients (median age, 51 years; range, 31 to 68 years) who underwent matched-sibling donor allo-HCT, administration of rituximab was associated with a low incidence of grade II-IV acute GVHD (aGVHD) of 20% and a 2-year disease-free survival rate of 84% [5]. A study by the same group in 47 consecutive patients with follicular NHL using a similar regimen (although with a slightly different rituximab administration schedule) found a PFS of 83% and an OS of 85% at a median follow-up of 60 months (range, 19 to 94 months) [33]. The incidence of grade II-IV aGVHD was only 11%, but rituximab did not affect the incidence of chronic GVHD (cGVHD), which was 60% [33]. The BMT CTN 0701 trial evaluating this regimen in relapsed follicular NHL to confirm the foregoing findings has recently completed accrual [33].

A similar approach that incorporates high-dose rituximab to fludarabine and cyclophosphamide in 39 patients with chronic lymphocytic leukemia (CLL) (74% with overexpression of ZAP-70) reported 4-year PFS of 44% and OS of 48% [34]. The incidence of grade II-IV aGVHD was 45%, notably higher than reported previously [5,33]. More frequent donor lymphocyte infusion (DLI) in the CLL study (36%) [34] versus only 2% in the follicular NHL study [33] might explain this difference, at least in part.

A phase 2 study by Kharfan-Dabaja et al. [35] combined CD4-guided lymphodepletion using pentostatin and pharmacokinetically targeted i.v. busulfan plus rituximab (only for CD20$^+$) in 42 patients, median age 53 years (range, 29 to 73 years), with various hematologic malignancies. Rituximab was administered to 33 patients (79%). All patients received peripheral blood stem cells. Updated results compiled after the 2011 annual American Society of Hematology meeting showed a 100-day and 2-year NRM of 2% and 17%, respectively [35]. All patients (100%) achieved ≥50% CD3$^+$ donor chimerism by day +28 (median, 87%). In disagreement with previous reports [5,33], the incidence of day +100 grade II-IV aGVHD was 59% (grade III-IV, 19%), and 2-year PFS and OS were 55% and 68%, respectively. This regimen resulted in early durable engraftment and low NRM. A higher number of alternative donors and perhaps the lower cumulative dose of rituximab used (1875 mg/m^2 versus 3375 mg/m^2) might explain the higher incidence of aGVHD [5,33-35].

Recently, Michallet et al. [36] combined fludarabine, 2 Gy TBI, and rituximab (375 mg/m^2 on day -5 and 500 mg/m^2 on days +1 and +8) in 40 patients with CLL age <65 years. One-year and 3-year NRM were 10% and 27%, respectively. The incidence of grade II-IV aGVHD was 44%, with a protective effect of rituximab ($P = .02$) based on univariate analysis. The probability of 5-year OS was 55%. The results of this and other studies are summarized in Table 2 [37,38].

Life-threatening complications associated with rituximab administration in allo-HCT recipients, including an increased risk of serious infections due to prolonged and profound cytopenias or persistent hypogammaglobulinemia, merit serious consideration [39]. Late-onset neutropenia has also been linked to rituximab administration, possibly related to arrest of maturation, apparently more likely in the presence of a particular polymorphism of FCγRIIIa (158 V/F) [40,41].

RADIOIMMUNOTHERAPY

Radioimmunotherapy (RIT) with mAbs (typically against CD20) conjugated to a radionuclide is effective against B cell NHL. Two agents are currently in clinical use for indolent

Table 1
Selected Studies Incorporating Rituximab to Auto-HCT

Study	Yr	Type (Median Follow-up)	N	Diagnosis	Addition of Rituximab to Regimens	Rituximab Dosage	Outcomes/Comments
Flinn et al. [23]*	2000	Single arm, phase 2 (240 days)	25	Follicular NHL: 44% MCL: 28% CLL/SLL: 20% Lymphoplasmacytic: 4% MZL: 4%	(1) Day 1 of cyclophosphamide mobilization chemotherapy (2) Seven days after platelet independence is achieved	(1) 375 mg/m^2 (2) 375 mg/m^2	All patients engrafted. Transient neutropenia noted. Six of 7 grafts PCR-negative.
Flohr et al. [25]	2002	Single arm, phase 2 (16 mo)	27	Follicular NHL: 44% MCL: 19% MZL: 7% DLBCL: 30%	(1) Day 1 of dexamethasone-BEAM† mobilization chemotherapy (2) Days -10 and -3 of various conditioning regimens	(1) 375 mg/m^2 (2) 375 mg/m^2	16-mo OS 95% and 16-mo PFS 77% in B cell NHL
Khouri et al. [26]‡	2005	Single arm, phase 2 (20 mo)	67	DLBCL: 61% Follicular NHL: 39%	(1) Day -1 and 7 days after mobilization chemotherapy (2) Days +1 and +8 after BEAM	(1) 375 mg/m^2 and 1000 mg/m^2 (2) 1000 mg/m^2	2-yr OS 80% and 2-yr disease-free survival 67% in aggressive B cell NHL
Tarella et al. [27]	2008	Multicenter, retrospective (7 yr)	349	DLBCL: 73% Follicular NHL: 27%	(1) Four doses before PBSC collection (2) Two additional doses after autologous HCT	(1) Not available (2) Not available	5-yr OS 69% versus 60% without rituximab
Hicks et al. [28]*‡	2008	Single arm, phase 2 (74.2 mo)	23	Relapsed follicular NHL: 100%	(1) Before or during granulocyte-colony stimulating factor administration for mobilization (2) Posttransplantation maintenance	(1) 375 mg/m^2 (2) Two 4-weekly at 375 mg/m^2 at 8 wks and 24 wks	77% achieved molecular remission after auto-HCT
Vose et al. [30]*‡	2011	Randomized, phase 3, multicenter (25.5 mo)	112	DLBCL: 100%	Days -19 and -12 of BEAM	375 mg/m^2	2-yr OS 65.6% and 2-yr PFS 48.6% in relapsed DLBC NHL

MZL indicates marginal-zone lymphoma; PBSC, peripheral blood stem cell; SLL, small lymphocytic lymphoma.

* Study reported a formal statistical design and analysis.

† Dexamethasone-BEAM consisted of oral dexamethasone 8 mg 3 times a day on days 1-10, BCNU 60 mg/m^2 on day 2, etoposide 75 mg/m^2 days 4-7, cytarabine 100 mg/m^2 2 times a day on days 4-7, and melphalan 20 mg/m^2 on day 3.

‡ Study formally stated and tested a hypothesis.

Table 2
Studies Incorporating Rituximab in Allo-HCT Conditioning Regimens

Study	Year	Type	N	Diagnosis	Donor Source	Preparative Regimen	Schedule of Rituximab Administration	Cumulative Rituximab Dose	GVHD Incidence	NRM	Survival Outcomes
Khouri et al. [5]	2001	Case series	20	Follicular NHL: 90%	MRD: 100%	FLU-CY	Day -6: 375 mg/m^2 Day +1: 1000 mg/m^2 Day +8: 1000 mg/m^2 Day +15: 1000 mg/m^2	3375 mg/m^2	Acute grade II-IV: 20% Chronic: 64%	10%	2-yr PFS: 84%
Khouri et al. [33]*†	2008	Single arm, phase 2	47	Follicular NHL: 100%	MRD: 96% MUD: 4%	FLU-CY	Day -13: 375 mg/m^2 Day -6: 1000 mg/m^2 Day +1: 1000 mg/m^2 Day +8: 1000 mg/m^2	3375 mg/m^2	Acute grade II-IV: 11% Chronic: 60%	15%	At a median follow-up of 60 mo: PFS: 83% OS: 85%
Khouri et al. [34]*	2007	Single arm, phase 2	39‡	CLL: 100%	MRD: 82% MUD: 8% Other: 10%	FLU-CY	Day -13: 375 mg/m^2 Day -6: 1000 mg/m^2 Day +1: 1000 mg/m^2 Day +8: 1000 mg/m^2	3375 mg/m^2	Acute grade II-IV: 45% Chronic extensive: 58%	26%	4-yr PFS: 44% 4-yr OS: 48%
Glass et al. [38]	2008	Randomized phase 2 (rituximab versus no rituximab)	65§	DLBCL: 53%	MRD: 29% MUD: 54% MMD: 17%	FLU-BU-CY ± ATG	Cycle 1, starting on day +21: weekly × 4 Cycle 2, starting on day +175: weekly × 4	3000 mg/m^2 (1500 mg/m^2 by day +100)	Acute grade II-IV: 73%	-	1-yr PFS: 39% 1-yr OS: 49%
Pidala et al. [37]	2011	Retrospective case series	19	CLL: 42% Follicular: 32% MCL: 16% DLBC: 11%	MRD: 42% MUD: 37% MMD: 21%	FLU-BU ± ATG	Day +1: 375 mg/m^2 Day +8: 375 mg/m^2	750 mg/m^2	Acute grade II-IV: 58% Chronic: 50%	-	1-yr OS: 67%
Kharfan-Dabaja et al. [35]*†	2011	Single arm, phase 2	42	CLL: 45% Follicular: 14% MCL: 10% DLBCL: 5% Transformed: 5% Others: 21%	MRD: 47% MUD: 43% MMD:10%	Pentostatin-BU¶	Day -21: 375 mg/m^2 Day -14: 375 mg/m^2 Day -7: 375 mg/m^2 Day +1: 375 mg/m^2 Day +8: 375 mg/m^2	1875 mg/m^2	Acute grade II-IV: 59%# Chronic: 69%#	100-day: 2%# 2-yr: 17%#	2-yr PFS: 55%# 2-yr OS: 68%#
Michallet et al. [36]*†	2013	Single arm, phase 2, multicenter	40	CLL: 100%	MRD: 100%	FLU-TBI	Day -5: 375 mg/m^2 Day +1: 500 mg/m^2 Day +8: 500 mg/m^2	1375 mg/m^2	Acute grade II-IV: 44% Chronic: 29%	1-yr: 10% 3-yr: 27%	5-yr event-free survival: 46% 5-yr OS: 55%

BU indicates busulfan; CY, cyclophosphamide; FLU, fludarabine; MMD, mismatched donor; MRD, matched-related donor; MUD, matched unrelated donor; (-), not reported/not extractable.

* Study reported a formal statistical design and analysis.

† Study formally stated and tested a hypothesis.

‡ Twenty-four patients had ZAP-70− expressing CLL.

§ Reported outcomes based on 59 evaluable cases only.

¶ Rituximab administered only to 33 patients (79%) with CD20$^+$-expressing lymphomas.

Outcome included all subjects.

NHL: yttrium-90 ibritumomab tiuxetan (^{90}Y-IT) and ^{131}I-T. Lymphoid malignancies are radiosensitive, and a distinct inverse relationship between relapse rate and the dose of external beam radiotherapy has been reported [42]. Although TBI has long been used for HCT conditioning in patients with NHL, TBI-based conditioning is associated with organ toxicity and secondary malignancies and often is not feasible in elderly patients and patients with significant comorbidities [43,44]. Limited nonhematologic toxicity and ability of radioimmunoconjugates to deliver targeted radiation provided the basis for developing RIT-based HCT conditioning regimens for NHL.

Two main approaches have evolved for applying RIT as HCT conditioning. One uses high-dose myeloablative RIT (with or without chemotherapy), and the other combines standard-dose RIT with HDT before auto-HCT or with RIC before allo-HCT.

High-Dose RIT for Auto-HCT Conditioning

Press et al. [45] pioneered the use of myeloablative RIT conditioning for auto-HCT [45]. In early, dose-finding, phase 1 studies of ^{131}I-T conditioning, the maximum tolerated dose (MTD) of radiation that was safely delivered to vital organs was 27 Gy. Further dosage escalation was limited by cardiopulmonary toxicities [45]. Several small phase 2 studies using high-dose RIT with ^{131}I-T alone, mainly in patients with chemosensitive relapsed B cell NHL, demonstrated 4-year PFS of 40% and OS of 65% (Table 3) [46-48], with acceptable toxicities. A combination of high-dose ^{131}I-T (delivering radiation doses up to 27 Gy to normal organs) and HDT as conditioning before auto-HCT [49,50] also appears to be feasible, with 3-year PFS and OS approaching 60% to 65% and 80% to 90%, respectively; these results compare favorably with outcomes with high-dose RIT conditioning alone [46-48]. However, because ^{131}I-T emits γ-radiation, its administration is complicated by prolonged patient isolation, special infusion equipment, caregiver/health care worker exposure precautions, and complex dosimetry facilities.

^{90}Y-IT, being a pure β-emitter, does not require prolonged patient isolation or strict contact precautions. Nademanee et al. [51], in a phase 1/2 study, combined ^{90}Y-IT RIT with HDT for auto-HCT in patients with B cell NHL and reported a 2-year PFS of 78% and OS of 92% [51]. Others have also reported encouraging outcomes in B cell NHL with high-dose ^{90}Y-IT–based conditioning, both with [52] and without [53,54] HDT (Table 3). Although these studies have established the feasibility of high-dose RIT conditioning in auto-HCT, they are limited by small sample size, heterogeneous NHL histologies, and remission status at transplantation. RIT conditioning was originally developed to extend HCT to otherwise ineligible candidates for HDT and autografting, owing either to advanced age or chemotherapy-unresponsive disease. However, the median patient age in most previous studies was <60 years, and most of the studies included chemotherapy-sensitive cases (Table 3). Retrospective data suggest the possible superiority of high-dose RIT conditioning over chemotherapy and/or radiation-containing conditioning [55]; however, no prospective RCTs have been performed to provide conclusive evidence of this. RIT-based auto-HCT in specialized centers is feasible and does not appear to be associated with higher-than-expected rates of secondary malignancies [56]; however, more data are needed to better define the subgroup most likely to benefit from this approach. In the absence of convincing data indicating that high-dose RIT conditioning can be administered without a meticulous and complex dosimetric approach, this modality likely will remain confined to centers with available expertise.

Standard-Dose RIT-Based Conditioning for Auto-HCT

To circumvent logistical challenges to the safe administration of high-dose RIT, investigators have combined standard-dose RIT with HDT to intensify auto-HCT conditioning (Table 4). A phase 1 study by Vose et al. [57] established the feasibility of combining ^{131}I-T with BEAM conditioning for auto-HCT in aggressive NHL. The MTD of ^{131}I-T was 0.75 Gy, with 3-year PFS and OS of 39% and 55%, respectively. Nonetheless, the myriad of subsequent published studies evaluating standard-dose RIT for auto-HCT (Table 4) are difficult to interpret (for routine clinical use) owing to the heterogeneity of RIT regimens used (^{131}I-T versus ^{90}Y-IT), histological subtypes of NHL, and disease status. Several uncontrolled, single-arm studies showed impressive outcomes for relapsed, chemosensitive DLBCL after RIT conditioning and auto-HCT [57-59]; however, the BMT-CTN 0401 trial, which randomized patients with chemosensitive-relapsed DLBCL to either ^{131}I-T–BEAM or rituximab-BEAM conditioning, demonstrated no benefit of RIT conditioning for disease control or survival [30]. Moreover, the French cooperative group study that randomized patients chemosensitive, relapsed aggressive NHL to conditioning with ^{90}Y-IT–BEAM or BEAM was closed prematurely because of slow accrual [60]. Despite the small sample size ($n = 43$), RIT-BEAM showed a trend for improved OS (91% versus 62%; $P = .05$), but at the cost of a higher rate of infection (27% versus 5%; $P = .05$) [60]. Whether the marginal benefit seen in the French study reflects better efficacy of ^{90}Y-IT compared with the ^{131}I-T used in the BMT-CTN 0401 study remains unknown. The published evidence currently does not support routine addition of standard-dose RIT to auto-HCT conditioning in patients with relapsed, chemosensitive DLBCL.

The European Mantle Cell Lymphoma Network's MCL-3 study added RIT to auto-HCT conditioning in patients with mantle cell lymphoma (MCL) not achieving a complete remission after first-line chemoimmunotherapy [61]. Compared with historical controls [62], however, no clear benefit of adding ^{90}Y-IT was observed. RIT as an auto-HCT conditioning component for patients with MCL undergoing up front transplantation cannot be considered a standard option at present.

Chemorefractory DLBCL has a poor prognosis [63]. Several studies have suggested encouraging outcomes in patients in this subgroup after RIT-based auto-HCT, with 2- to 3-year PFS and OS of 39% to 63% and 55% to 67%, respectively [57,58,64]. Similarly, excellent outcomes in indolent NHL after RIT-based auto-HCT have been reported [65,66]. We emphasize that no randomized data exist demonstrating the superiority of RIT-based conditioning for refractory aggressive or indolent NHL. Accordingly, the role of standard-dose RIT conditioning for auto-HCT remains a valid research question.

RIT-Based Conditioning for Allo-HCT

It is clear that HDT (with or without RIT) followed by auto-HCT does not provide durable remissions in patients with heavily pretreated, chemorefractory, or bulky NHL [67]. In these poor-risk cases, especially those of advanced age or with comorbidities, RIC allo-HCT is frequently considered, aiming at a potentially curative graft-versus-lymphoma (GVL) effect. Lack of intensive chemotherapy and/or

Table 3
Prospective Studies Evaluating the Role of High-Dose Radioimmunotherapy-Based Conditioning in Auto-HCT

Study	Year	Type (median follow-up)	n	Age, Years Median (Range)	Histology	Conditioning	TRM	PFS	OS	Comments
Press et al. [45]*	1993	Phase 1 (-)	24	47	B cell NHL	^{131}I-T or ^{131}I anti- CD37	-	-	21 mo (median)	MTD was 27 Gy of radiation to normal vital organs. Cardiopulmonary toxicity was dose-limiting.
Liu et al. [47] Press et al. [46]	1998 1995	Phase 1/2 (42 mo)	29	46 (24-59)	B cell NHL	^{131}I-T	-	42% (4 yr)	68% (4 yr)	In phase I of the study, 0.35, 1.7, or 7 mg/kg of CD20 antibody was trace-labeled with ^{131}I. Goal was to deliver $\leq$27 Gy to normal organs.
Kaminski et al. [48]	1996	Phase 1 (-)	34	52 (27-74)	B cell NHL	^{131}I-T	-	-	-	MTD was 75 cGy whole-body radiation.
Press et al. [49]*	2000	Phase 1/2 (-)	52	47 (34-58)	FL, MCL, Tx-NHL	^{131}I-T + CY/VP-16	-	68% (2 yr)	83% (2 yr)	Patients received 1.7 mg/kg of tositumomab labeled with an amount of ^{131}I calibrated to a target dose of 20-27 Gy to vital normal organs.
Gopal et al. [50]	2002	Phase 2 (-)	16	54 (35-59)	MCL	^{131}I-T + CY/VP-16	-	61% (3 yr)	93% (3 yr)	Patients received 1.7 mg/kg of tositumomab labeled with an amount of ^{131}I calibrated to a target dose of 25 Gy to vital normal organs. 50% had refractory disease.
Nademanee et al. [51]	2005	Phase 1/2 (22 mo)	31	51 (25-59.6)	FL, DLBCL, MCL	^{90}Y-IT + CY/VP-16	3%	78% (2 yr)	92% (2 yr)	^{90}Y dose calibrated to maintain normal organ dose <1000 cGy. Median delivered dose was 71.6 mCi. All patients were aged <60 yr.
Ferrucci et al. [54]	2007	Phase 1 (-)	13	62 (28-73)	FL, DLBCL, Tx-NHL, MCL	^{90}Y-IT	-	-	-	One patient developed MDS.
Devizzi et al. [53]	2008	Phase 2 (30 mo)	30	62 (29-76)	B cell NHL	^{90}Y-IT	-	69% (2.5 yr)	87% (2.5 yr)	All patients had uniform induction and mobilization. Included patients in first remission.
Winter et al. [52]*	2009	Phase 1 (33 mo)	44	54 (25-73)	FL, DLBCL, Tx-NHL, MCL	^{90}Y-IT + BEAM	-	43% (3 yr)	60% (3 yr)	30% had refractory disease. 15 Gy was the recommended maximum absorbed dose to vital normal organs.
Hohloch et al. [105]*	2011	Phase 2 (50.4 mo)	16	55 (45-63)	B cell NHL	BEAM for first auto-HCT; ^{131}I-rituximab for second auto-HCT	33% after second auto-HCT	64% (4 yr)	67% (4 yr)	12% had refractory disease. TRM was high after tandem auto-HCT.
Gopal et al. [70]†	2011	Phase 1 (30 mo)	36	65 (60-76)	B cell NHL	^{131}I-T + fludarabine	7% (3-yr)	53% (3 yr)	54% (3 yr)	12% had refractory disease. ^{131}I was calibrated to deliver a target dose of 27 Gy to vital normal organs.

CY indicates cyclophosphamide; FL, follicular lymphoma; MZL, marginal-zone lymphoma; Tx-NHL, transformed NHL; R, rituximab; TRM, treatment-related mortality; VP-16, etoposide; (-), not reported/not extractable.
* Study reported a formal statistical design and analysis.
† Study formally stated and tested a hypothesis.

Table 4
Prospective Studies Evaluating the Role of Standard-Dose Radioimmunotherapy-Based Conditioning in Auto-HCT

Study	Year	Type (Median Follow-up)	N	Age, Years, Median (Range)	Histology	Conditioning	TRM	PFS	OS	Comments
Vose et al. [57]*	2005	Phase 1 (18.4 mo)	23	51 (26-65)	Grade 3 FL, DLBCL, MCL	^{131}I-T + BEAM	—	39% (3-yr)	55% (3 yr)	52% of patients had refractory disease; 2 patients developed MDS; MTD of ^{131}I-T was 0.75 Gy.
Shimoni et al. [58]	2007	Phase 2 (17 mo)	23	55 (35-66)	DLBCL, Tx-NHL, MCL	^{90}Y-IT + BEAM†	17% (2 yr)	52% (2 yr)	67% (2 yr)	All patients were chemorefractory.
Krishnan, et al. [106]	2008	Phase 2 (-)	41	59.6 (19-78)	FL, DLBCL, Tx-NHL, MCL	^{90}Y-IT + BEAM†	0% (day 100)	70% (2 yr)	89% (2 yr)	29% had refractory disease; PFS of PET-CT^{+} patients was 45%.
Decaudin et al. [65]*	2011	Phase 2 (28 mo)	77	-	FL, MZL	^{90}Y-IT + BEAM‡	0% (day 100)	63% (2 yr)	97% (2 yr)	All patients were chemosensitive; 2 s cancers were seen.
Zipp et al. [66]	2011	Phase 2 (56 mo)	36	-	DLBCL, FL	^{90}Y-IT + BEAM†	-	60%-78% (5 yr)	60%-76% (5 yr)	8% s cancers at 5 yr.
Vose et al. [30]*§	2011	Phase 3 (25.5 mo)	224	56.8	DLBCL	^{131}I-T + BEAM versus R-BEAM	4.9% versus 4.1% (2 yr)	48% versus 49% (2 yr)	60% versus 66% (2 yr)	BMT-CTN Trial 0401
Shimoni et al. [60]*§	2012	Phase 3 (29 mo)	22 versus 21	55 (23-67)	Aggressive NHL	^{90}Y-IT + BEAM versus BEAM†	-	59% versus 37% (2 yr)	91% versus 62% (2 yr)	All patients were chemosensitive; similar engraftment kinetics in the 2 groups, but infections in RIT group; trend toward improved OS with RIT.
Arne et al. [61]§	2012	Phase 2 (3.2 yr)	69	57 (28-65)	MCL	^{90}Y-IT + BEAM†	3%	55% (5 yr)	71% (5 yr)	Included only MCL not in CR after first-line therapy; no benefit of RIT over historical controls.
Briones et al. [64]	2012	Phase 2 (22.7 mo)	30	53 (25-67)	DLBCL	^{90}Y-IT + BEAM†	-	63% (2 yr)	65% (2 yr)	All patients were chemorefractory.
Vose et al. [59]*	2013	Phase 2 (6 yr)	40	54 (26-75)	DLBCL	^{131}I-T + BEAM	-	70% (5 yr)	72% (5 yr)	All patients were chemosensitive; 5 secondary malignancies were reported.

FL indicates follicular lymphoma; MZL, marginal-zone lymphoma; Tx-NHL, transformed NHL; R, rituximab; TRM, treatment-related mortality; (-), not reported/not extractable.

* Study reported a formal statistical design and analysis.

† ^{90}Y-IT dose: 0.4 mCi/kg.

‡ ^{90}Y-IT dose: 0.3-0.4 mCi/kg.

§ Study formally stated and tested a hypothesis.

radiotherapy in RIC regimens is associated with higher risk of relapse, however, especially in refractory or bulky disease [68]. This is because disease control in low-intensity allo-HCT relies heavily on the GVL effect, which might take months to establish [69]. RIT's lack of significant nonhematologic toxicities and potential efficacy in chemotherapy-refractory B cell NHL provided the rationale for combining this modality with RIC allografts to provide effective cytoreduction while GVL ensues [70].

Shimoni et al. [71] demonstrated the feasibility of combining ^{90}Y-IT RIT with fludarabine-based RIC in 12 chemorefractory patients undergoing allo-HCT (Table 5). In a large prospective study, German investigators combined ^{90}Y-IT RIT with fludarabine and low-dose TBI-containing nonmyeloablative conditioning [72]. The majority of their patients (85%) had chemosensitive disease; 2-year PFS was 43%, with a high rate of aGVHD and a 2-year NRM of 45%. Conversely, Gopal et al. [70], using a similar regimen in chemorefractory cases (85%), reported a 2-year PFS of 31%, with an NRM of 16%. On multivariate analysis, patients with indolent NHL had a superior OS [70]. This observation was confirmed in the study of Khouri et al. [73], where an RIT-based nonmyeloablative conditioning resulted in 3-year PFS and OS >80% in patients with follicular NHL, with low NRM.

It is important to note that although the aforementioned studies have established the feasibility of combining RIT with RIC regimens before allo-HCT, there are no RCTs to establish the superiority of these regimens over RIT-free regimens. Follow-up in published studies was relatively short, and the majority of studies included a variety of histologies. Rates of disease control, with one exception [73], appeared modest at best. The sole published study evaluating higher-than-conventional doses of ^{90}Y-IT in RIC allo-HCT (Table 5) showed no clear evidence of improved disease control with more intense RIT, despite treating mostly patients with chemosensitive NHL [74]. The low PFS might be related to previous rituximab exposure and CD20 site blocking, limiting optimal binding of ^{90}Y-IT [70,75]. Whether restricting administration of ^{90}Y-IT RIC only to cases with previous limited rituximab exposure, targeting an alternative tumor surface antigen with novel radiolabelled antibodies [76], or pursuing pretargeted RIT techniques [77] would improve outcomes remains unclear. Until randomized data establishing the superiority of RIT-based conditioning regimens in allo-HCT become available, this strategy should be considered only within the context of clinical trials.

ALEMTUZUMAB

Alemtuzumab is a humanized mAb against the CD52 antigen, expressed mainly on normal B and T lymphocytes, macrophages, monocytes, natural killer cells, and some dendritic cells [78-80], that is approved for the treatment of CLL [81,82]. Alemtuzumab has been incorporated in conditioning regimens for RIC allo-HCT, mostly to decrease the incidence and severity of aGVHD and cGVHD and to reduce graft rejection [83,84].

The efficacy of alemtuzumab has been demonstrated in both matched related donor and matched unrelated donor allografting [85,86]. Kottaridis et al. [85] evaluated a regimen of fludarabine, melphalan, and alemtuzumab in 44 patients with various hematologic malignancies. Alemtuzumab 30 mg/day i.v. was administered for 5 days. Forty-two of 43 evaluable subjects (98%) achieved sustained engraftment. Full donor chimerism was reported in 18 (58%) of 31

Table 5
Prospective Studies Evaluating the Role of Radioimmunotherapy-Based Conditioning in Allo-HCT

Study	Year	Type (Median Follow-up)	N	Age, yrs (range)	Histology	Conditioning	NRM	PFS	OS	Comments
Shimoni et al. [71]	2008	Phase 2 (21 mo)	12	54 (37-62)	B cell NHL	^{90}Y-IT + FLU/BU or FLU/MEL*	42% (2 yr)	33% (2 yr)	33% (2 yr)	All patients had refractory disease; high rate of grade II-IV aGVHD (67%).
Nademanee et al. [107]	2008	Phase 2 (-)	13	55 (27-67)	B cell NHL	^{90}Y-IT + FLU/MEL*	31% (1 yr)	69% (1 yr)	69% (1 yr)	Ten patients had refractory disease.
Bethge et al. [72]†	2010	Phase 2 (22 mo)	40	58 (34-68)	Indolent NHL and MCL	^{90}Y-IT + FLU/TBI (2 Gy)*	45% (2 yr)	43% (2 yr)	51% (2 yr)	15% had refractory disease; 13 patients received an MRD allograft.
Gopal et al. [70]†‡	2011	Phase 2 (1.7 yr)	45	58 (29-69)	B cell NHL	^{90}Y-IT + FLU/TBI (2 Gy)*	16% (2 yr)	31% (2 yr)	54% (2 yr)	85% had refractory disease; 38% received an MRD allograft; indolent NHL was associated with better OS.
Khouri et al. [73]	2012	Phase 2 (33 mo)	26	55 (29-66)	FL	^{90}Y-IT + FLU/CY*	8% (1 yr)	85% (3 yr)	88% (3 yr)	38% had refractory disease; 58% received an MRD allograft.
Bethge et al. [74]	2012	Phase 2 (36 mo)	20	51 (29-69)	B cell NHL	^{90}Y-IT + FLU/MEL + alemtuzumab§	30% (3 yr)	20% (3 yr)	20% (3 yr)	Five patients received an MRD allograft; 1 patient had refractory disease.

BU indicates busulfan; CY, cyclophosphamide; FL, follicular lymphoma; FLU, fludarabine; MEL, melphalan; MRD, matched related donor; (-), not reported/not extractable.
* ^{90}Y-IT dose: 0.4 mCi/kg (32 mCi maximum dose allowed).
† Study reported a formal statistical design and analysis.
‡ Study formally stated and tested a hypothesis.
§ ^{90}Y-IT dose: 0.6 or 0.8 mCi/kg.

evaluable subjects. The incidence of grade II aGVHD was 5%, with no reported grade III to IV aGVHD. NRM at 1 year was 11%. There were 7 relapses or progression, for which DLI administration did not improve outcomes [85]. Delgado et al. [87], in a study of 41 patients with CLL, found a 27% risk of relapse after alemtuzumab-based regimens for allo-HCT. NRM was 26%, mostly associated with infections [87]. The rate of aGVHD was 41% (10% grade III-IV). These findings demonstrate that depletion of alloreactive T cells with alemtuzumab reduces the incidence and severity of aGVHD, but at the cost of increased risk of relapse and opportunistic infections.

Administration of DLI as prophylaxis to prevent relapse after T cell–depleted allografts has proven effective, particularly in cases of mixed donor chimerism [88,89]. Peggs et al. [88] reported encouraging outcomes in 22 patients with relapsed Hodgkin lymphoma who received an alemtuzumab-based regimen and dose-escalated DLI for mixed donor chimerism. Nineteen of the 22 patients (86%) converted to full donor chimerism, and the incidence of relapse was 5% at 4 years. NRM attributable to DLI was 7%, attributed mainly to aGVHD.

A major concern related to alemtuzumab-induced T cell depletion is the potential development of opportunistic infections. For instance, CMV reactivation has been reported in up to 85% of patients at risk for CMV infection [86]. Preemptive CMV therapy is effective in this setting, but the development of deadly CMV infection remains a risk [86]. Chakraverty et al. [86] reported an actuarial probability of CMV disease of 6.4% at 12 months in high-risk and intermediate-risk cases. An increased risk of bacterial and fungal infections has also been associated with alemtuzumab-based regimens [87]. Use of alemtuzumab-based regimens for allo-HCT remains a reasonable option associated with low NRM, but at the cost of a high risk of relapse and serious opportunistic infections.

GEMTUZUMAB OZOGAMICIN

Gemtuzumab ozogamicin (GO) is a humanized calicheamicin-conjugated mAb targeting CD33 [90]. Previous exposure to GO increases the risk of hepatic veno-occlusive disease, particularly in the myeloablative HCT setting [91]. GO was withdrawn from the market in 2010 owing to a lack of efficacy and safety concerns.

de Lima et al. [92] conducted a phase 1/2 trial combining GO with a fludarabine-melphalan RIC allo-HCT regimen in patients with $CD33^+$ AML/MDS. GO was administered on day -12 of conditioning. NRM (100-day) was 15%. Bornhäuser et al. [93] administered GO 6 mg/m^2 on day -21 and 3 mg/m^2 on day -14 before various fludarabine-based or TBI-based RIC allo-HCT regimens in 31 patients with relapsed AML. NRM was 22% at day +100. Two-year OS was 39%, and PFS was 35%. A phase 1 trial of GO on day -14 combined with busulfan and cyclophosphamide myeloablative conditioning in children with AML undergoing allo-HCT using mainly umbilical cord cells reported a 100-day NRM of 0% [94]. A phase 2 study using GO 7.5 mg/m^2 in combination with myeloablative conditioning in children with AML is ongoing [94]. Overall, the combination of GO and RIC regimens for allo-HCT appears feasible; unfortunately, this drug is not commercially available.

EPRATUZUMAB

The CD22 antigen, a member of the immunoglobulin superfamily, is a 135-kDa type I transmembrane phosphoglycoprotein with B cell–restricted expression involved in B cell receptor signaling, B cell survival, and homing [95,96]. The literature suggests that most B cell hematologic malignancies express CD22, making it an attractive therapeutic target. Epratuzumab is a humanized anti-CD22 mAb that has shown activity in preclinical and clinical investigations [96]. An antibody–drug conjugate targeting CD22, inotuzumab ozogamicin, consisting of a derivative of calicheamicin linked to a humanized mAb against CD22, has shown promising activity in relapsed B cell NHL [97]. There are no published reports on epratuzumab- or inotuzumab ozogamicin–containing regimens for HCT.

DISCUSSION

The incorporation of mAbs into HCT conditioning regimens has occurred at a slower pace than the combination of mAbs with conventional chemotherapies, owing to the immunologic complexities, particularly in the allo-HCT setting. Strategies to improve efficacy as well as our understanding of the role of B cells in the pathogenesis of GVHD will lead to the incorporation of rituximab in allo-HCT preparative regimens with a dual goal of improving responses and reducing NRM [98].

In a phase 2 randomized study, Glass et al. [38] reported an interim analysis that found no benefit of adding rituximab to an intermediate-intensity regimen for allo-HCT for aggressive lymphomas (Table 2) in terms of the incidence of GVHD, PFS, or OS. To our knowledge, that study still has not been published in final, complete form more than 4 years later [38]. Accordingly, published RCTs are lacking, and the existing evidence, with few exceptions [36], is from single-arm studies or case series from single institutions [5,33-35,37]. Of the studies summarized in Table 2, only 3 single-arm phase 2 studies focused on a particular disease [33,34,36]. Two of those studies, which focused on CLL, used different conditioning regimens and rituximab doses and administration schedules [34,36], clearly limiting our ability to compare outcomes of these trials. Thus, the optimal dose and administration schedule remain unknown, with the allo-HCT literature describing cumulative doses ranging from 750 to 3375 mg/m^2 (Table 2).

Although results to date are encouraging, several limitations must be taken into account, including the nonrandomized nature of the studies, a bias favoring enrollment of younger patients, and subjectivity when assigning GVHD grading, among others. In addition, reported severe, prolonged cytopenias with the addition of rituximab in allo-HCT conditioning warrant careful prospective investigation to clearly define rituximab's therapeutic index in this setting. Post–allo-HCT rituximab administration for B cell depletion shows promise in modulating the incidence and intensity of cGVHD, which might further improve long-term NRM [99,100]. For allo-HCT, RIT-based conditioning holds great promise as a modality to provide adequate tumor control with low NRM, with curative GVL effects ensuing, but this approach remains experimental at present. The development of RIT targeting alternative tumor surface antigens [76] or pretargeted RIT techniques could further improve post–allo-HCT outcomes [77].

In the auto-HCT setting, no RCTs have been published comparing the addition of rituximab to HDT versus HDT alone. Evidence supporting a benefit of adding rituximab is purportedly related to *in vivo* purging of B cell infusates [101]. Moreover, a large multicenter RCT failed to demonstrate a benefit of adding ^{131}I-T vis-à-vis rituximab to BEAM [30]. One major concern is the choice of rituximab-BEAM as

the control arm; data supporting this arm as a control have been based on nonrandomized or registry data. The results of BMT-CTN 0401 cast serious doubts on the future of RIT conditioning in auto-HCT. The incorporation of novel antibodies (eg, MEDI-551, epratuzumab, ofatumumab, brentuximab vedotin, GA101) in auto-HCT conditioning regimens to improve disease control and reduce relapse is an area of interest.

Major concerns with using alemtuzumab in allo-HCT conditioning include prolonged lymphopenia and impaired immune reconstitution, high risk of relapse, and serious opportunistic infections. Strategies incorporating DLI to reduce disease relapse are logical and apparently effective [89]. Strategies that potentially could help reduce the incidence of infections such as CMV are emerging and might offer added benefits to preemptive CMV treatment approaches [102]. The optimal dose and administration schedule of alemtuzumab to maintain effective GVHD prophylaxis while avoiding prolonged immune paresis remain elusive.

Pertaining to myeloid malignancies, GO is the only mAb that has been incorporated into allo-HCT preparative regimens for AML. Unfortunately, this agent is not commercially available at present. A novel anti-CD33 immunotoxin, humanized mAb M195 conjugated to recombinant gelonin (HUM-195/rGEL), has been evaluated in a phase 1 study, and is shown to be safe when administered in multidose cycles [103]; this agent has not been studied in allo-HCT regimens, however.

It is anticipated that additional mAbs will become available in the near future and will be incorporated into HCT conditioning regimens once their safety and clinical efficacy is demonstrated.

RECOMMENDATIONS AND FUTURE DIRECTIONS

Despite the aforementioned limitations, which mostly relate to the lack of RCTs (with the exception of BMT CTN 0401), multiple factors may be considered in the decision of whether to include mAbs in conditioning regimens for HCT. First, some centers incorporate rituximab as part of conditioning regimens for auto-HCT based on improved outcomes from phase 2 or registry studies compared with historical controls. RCT data are lacking, however. Careful consideration, assessment, and discussion with patients are required before including rituximab in a conditioning regimen for auto-HCT, given the risk of prolonged cytopenias and consequent increased risk of late infections in this setting. More data are needed to determine the optimal dose and administration schedule of rituximab in this setting. Although continuous detection of circulating rituximab may confer a protective effect against disease relapse, a recent randomized study showed no benefit of rituximab maintenance after auto-HCT in patients with relapsed DLBC NHL [104].

Second, randomized data do not support the use of standard-dose RIT in combination with HDT conditioning for either auto- or allo-HCT in patients with chemosensitive DLBCL and MCL at the present time. The use of standard-dose RIT in other lymphoid histologies remains investigational. High-dose RIT (with or without HDT) performed in centers with available expertise and dosimetric facilities appears to be a valid option for patients with advance and/or chemorefractory lymphoid malignancies, but randomized data from this setting are lacking.

Third, the feasibility of incorporating rituximab in allo-HCT conditioning regimens is supported mainly by small, single-arm phase 2 studies, mostly from single institutions. A preparative chemoimmunotherapy regimen of fludarabine and cyclophosphamide plus rituximab in patients with follicular NHL may be beneficial, as supported by long-term follow-up data with encouraging outcomes, albeit nonrandomized [33]. The optimal rituximab dose and administration schedule remain subjects of research and will be best addressed within the context of a prospective randomized multicenter trial targeting an individual lymphoma subtype. Caution is advised when extrapolating data across different diseases and/or preparative regimens. Moreover, patients must be informed of the potential for serious infectious complications associated with the use of rituximab in the allograft setting, as well as the need for careful, long-term monitoring of immune reconstitution.

Fourth, there are no randomized data supporting T cell depletion using alemtuzumab as part of an allo-HCT preparative regimen. Given the reduced risk of GVHD, the use of alemtuzumab might be considered in matched unrelated donor or partially mismatched donor allografting, at the cost of increased risk of disease relapse or complications from CMV and other serious infections. Finally, we emphasize that enrollment in clinical trials remains the most desirable choice whenever available. Future trials incorporating these or other mAbs should focus on the development of disease-specific regimens, preferably in the context of multicenter prospective randomized trials with survival as the most important endpoint, facilitated through networks such as BMT CTN.

ACKNOWLEDGMENTS

Financial disclosure: M.A.K.-D. served as a member of the Genzyme speakers' bureau. None of the other authors has any conflict of interest to report.

REFERENCES

1. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*. 1997;90:2188-2195.
2. Baselga J, Norton L, Albanell J, et al. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu-overexpressing human breast cancer xenografts. *Cancer Res*. 1998;58:2825-2831.
3. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol*. 2003;21:60-65.
4. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med*. 2002;346:235-242.
5. Khouri IF, Saliba RM, Giralt SA, et al. Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. *Blood*. 2001;98:3595-3599.
6. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, et al. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2009;15:1005-1013.
7. Kharfan-Dabaja MA, Cutler CS. Rituximab for prevention and treatment of graft-versus-host disease. *Int J Hematol*. 2011;93:578-585.
8. Gómez-Almaguer D, Ruiz-Argüelles GJ, del Carmen Tarín-Arzaga L, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2008;14:10-15.
9. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540-1545.
10. Friedberg JW, Neuberg D, Stone RM, et al. Outcome in patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol*. 1999;17:3128-3135.

11. Caballero MD, Rubio V, Rifon J, et al. BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. *Bone Marrow Transplant*. 1997; 20:451-458.
12. de Magalhaes-Silverman M, Lister J, Rybka W, et al. Busulfan and cyclophosphamide (BU/CY2) as preparative regimen for patients with lymphoma. *Bone Marrow Transplant*. 1997;19:777-781.
13. Escalon MP, Stefanovic A, Venkatraman A, et al. Autologous transplantation for relapsed non-Hodgkin's lymphoma using intravenous busulfan and cyclophosphamide as conditioning regimen: a single center experience. *Bone Marrow Transplant*. 2009;44:89-96.
14. Hanel M, Kroger N, Sonnenberg S, et al. Busulfan, cyclophosphamide, and etoposide as high-dose conditioning regimen in patients with malignant lymphoma. *Ann Hematol*. 2002;81:96-102.
15. Schiffman KS, Bensinger WI, Appelbaum FR, et al. Phase II study of high-dose busulfan, melphalan and thiotepa with autologous peripheral blood stem cell support in patients with malignant disease. *Bone Marrow Transplant*. 1996;17:943-950.
16. Stiff P, Dahlberg S, Forman S, et al. Autologous bone marrow transplantation for patients with relapsed or refractory diffuse aggressive non-Hodgkin's lymphoma: value of augmented preparative regimens. A Southwest Oncology Group trial. *J Clin Oncol*. 1998;16:48-55.
17. Gulati S, Shank B, Black P, et al. Autologous bone marrow transplantation for patients with poor-prognosis lymphoma. *J Clin Oncol*. 1988;6:1303-1313.
18. Jagannath S, Dicke K, Armitage J, et al. High-dose cyclophosphamide, carmustine, and etoposide and autologous bone marrow transplantation for relapsed Hodgkin's disease. *Ann Intern Med*. 1986;104: 163-168.
19. Wang E, Chen Y, Corringham S, et al. High-dose CEB versus BEAM with autologous stem cell transplant in lymphoma. *Bone Marrow Transplant*. 2004;34:581-587.
20. Hoerr AL, Gao F, Hidalgo J, et al. Effects of pretransplantation treatment with rituximab on outcomes of autologous stem-cell transplantation for non-Hodgkin's lymphoma. *J Clin Oncol*. 2004;22: 4561-4566.
21. Vose JM, Link BK, Grossbard ML, et al. Long-term update of a phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2005;46:1569-1573.
22. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. 2004;103:3684-3688.
23. Flinn IW, O'Donnell PV, Goodrich A, et al. Immunotherapy with rituximab during peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. *Biol Blood Marrow Transplant*. 2000;6: 628-632.
24. Horwitz SM, Negrin RS, Blume KG, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Blood*. 2004;103:777-783.
25. Flohr T, Hess G, Kolbe K, et al. Rituximab in vivo purging is safe and effective in combination with CD34-positive selected autologous stem cell transplantation for salvage therapy in B-NHL. *Bone Marrow Transplant*. 2002;29:769-775.
26. Khouri IF, Saliba RM, Hosing C, et al. Concurrent administration of high-dose rituximab before and after autologous stem-cell transplantation for relapsed aggressive B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2005;23:2240-2247.
27. Tarella C, Zanni M, Magni M, et al. Rituximab improves the efficacy of high-dose chemotherapy with autograft for high-risk follicular and diffuse large B-cell lymphoma: a multicenter Gruppo Italiano Terapie Innnovative nei linfomi survey. *J Clin Oncol*. 2008;26:3166-3175.
28. Hicks LK, Woods A, Buckstein R, et al. Rituximab purging and maintenance combined with auto-SCT: long-term molecular remissions and prolonged hypogammaglobulinemia in relapsed follicular lymphoma. *Bone Marrow Transplant*. 2009;43:701-708.
29. Couriel D, Saliba R, Hicks K, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. *Blood*. 2004;104:649-654.
30. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 Trial. *J Clin Oncol*. 2013; 31:1662-1668.
31. Kharfan-Dabaja MA, Pidala J, Kumar A, et al. Comparing efficacy of reduced-toxicity allogeneic hematopoietic cell transplantation with conventional chemo-(immuno) therapy in patients with relapsed or refractory CLL: a Markov decision analysis. *Bone Marrow Transplant*. 2012;47:1164-1170.
32. Kharfan-Dabaja MA, Anasetti C, Santos ES. Hematopoietic cell transplantation for chronic lymphocytic leukemia: an evolving concept. *Biol Blood Marrow Transplant*. 2007;13:373-385.
33. Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood*. 2008;111:5530-5536.
34. Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. *Br J Haematol*. 2007;137:355-363.
35. Kharfan-Dabaja MA, Anasetti C, Fernandez HF, et al. Phase II study of CD4+guided pentostatin lymphodepletion and pharmacokinetically-targeted busulfan as conditioning for hematopoietic cell allografting. *Biol Blood Marrow Transplant*. 2013;19:1087-1093.
36. Michallet M, Socié G, Mohty M, et al. Rituximab, fludarabine, and total body irradiation as conditioning regimen before allogeneic hematopoietic stem cell transplantation for advanced chronic lymphocytic leukemia: long-term prospective multicenter study. *Exp Hematol*. 2013;41:127-133.
37. Pidala J, Roman-Diaz J, Kim J, et al. Targeted IV busulfan and fludarabine followed by post-allogeneic hematopoietic cell transplantation rituximab demonstrate encouraging activity in $CD20^{+}$ lymphoid malignancies without increased risk of infectious complications. *Int J Hematol*. 2011;93:206-212.
38. Glass B, Hasenkamp J, Gorlitz A, et al. Rituximab for graft-versus-host-disease-prophylaxis after allogeneic stem cell transplantation given as treatment of high-risk relapse of aggressive lymphoma: results of a randomized Phase II study. *ASH Annual Meeting Abstracts*. 2008;112: 1974.
39. McIver Z, Stephens N, Grim A, Barrett AJ. Rituximab administration within 6 months of T cell–depleted allogeneic SCT is associated with prolonged life-threatening cytopenias. *Biol Blood Marrow Transplant*. 2010;16:1549-1556.
40. Tesfa D, Gelius T, Sander B, et al. Late-onset neutropenia associated with rituximab therapy: evidence for a maturation arrest at the (pro)myelocyte stage of granulopoiesis. *Med Oncol*. 2008;25: 374-379.
41. Li SC, Chen YC, Evens AM, et al. Rituximab-induced late-onset neutropenia in newly diagnosed B-cell lymphoma correlates with Fc receptor FcγRIIIa 158(V/F) polymorphism. *Am J Hematol*. 2010;85: 810-812.
42. Fuks Z, Kaplan HS. Recurrence rates following radiation therapy of nodular and diffuse malignant lymphomas. *Radiology*. 1973;108: 675-684.
43. Montoto S, Canals C, Rohatiner AZ, et al. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. *Leukemia*. 2007;21:2324-2331.
44. Gisselbrecht C, Vose J, Nademanee A, et al. Radioimmunotherapy for stem cell transplantation in non-Hodgkin's lymphoma: in pursuit of a complete response. *Oncologist*. 2009;14(Suppl 2):41-51.
45. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. *N Engl J Med*. 1993;329:1219-1224.
46. Press OW, Eary JF, Appelbaum FR, et al. Phase II trial of ^{131}I-B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. *Lancet*. 1995;346:336-340.
47. Liu SY, Eary JF, Petersdorf SH, et al. Follow-up of relapsed B-cell lymphoma patients treated with iodine-131–labeled anti-CD20 antibody and autologous stem-cell rescue. *J Clin Oncol*. 1998;16: 3270-3278.
48. Kaminski MS, Zasadny KR, Francis IR, et al. Iodine-131 anti-B1 radioimmunotherapy for B-cell lymphoma. *J Clin Oncol*. 1996;14: 1974-1981.
49. Press OW, Eary JF, Gooley T, et al. A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. *Blood*. 2000;96:2934-2942.
50. Gopal AK, Rajendran JG, Petersdorf SH, et al. High-dose chemoradioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. *Blood*. 2002;99:3158-3162.
51. Nademanee A, Forman S, Molina A, et al. A phase 1/2 trial of high-dose yttrium-90–ibritumomab tiuxetan in combination with high-dose etoposide and cyclophosphamide followed by autologous stem cell transplantation in patients with poor-risk or relapsed non-Hodgkin lymphoma. *Blood*. 2005;106:2896-2902.
52. Winter JN, Inwards DJ, Spies S, et al. Yttrium-90 ibritumomab tiuxetan doses calculated to deliver up to 15 Gy to critical organs may be safely combined with high-dose BEAM and autologous transplantation in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:1653-1659.
53. Devizzi L, Guidetti A, Tarella C, et al. High-dose yttrium-90–ibritumomab tiuxetan with tandem stem-cell reinfusion: an outpatient preparative regimen for autologous hematopoietic cell transplantation. *J Clin Oncol*. 2008;26:5175-5182.
54. Ferrucci PF, Vanazzi A, Grana CM, et al. High-activity ^{90}Y-ibritumomab tiuxetan (Zevalin) with peripheral blood progenitor cell support in patients with refractory/resistant B-cell non-Hodgkin lymphomas. *Br J Haematol*. 2007;139:590-599.

55. Gopal AK, Rajendran JG, Gooley TA, et al. High-dose [^{131}I]tositumomab (anti-CD20) radioimmunotherapy and autologous hematopoietic stem-cell transplantation for adults > or = 60 years old with relapsed or refractory B-cell lymphoma. *J Clin Oncol*. 2007;25:1396-1402.
56. Guidetti A, Carlo-Stella C, Ruella M, et al. Myeloablative doses of yttrium-90–ibritumomab tiuxetan and the risk of secondary myelodysplasia/acute myelogenous leukemia. *Cancer*. 2011;117:5074-5084.
57. Vose JM, Bierman PJ, Enke C, et al. Phase I trial of iodine-131 tositumomab with high-dose chemotherapy and autologous stem-cell transplantation for relapsed non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23:461-467.
58. Shimoni A, Zwas ST, Oksman Y, et al. Yttrium-90–ibritumomab tiuxetan (Zevalin) combined with high-dose BEAM chemotherapy and autologous stem cell transplantation for chemo-refractory aggressive non-Hodgkin's lymphoma. *Exp Hematol*. 2007;35:534-540.
59. Vose JM, Bierman PJ, Loberiza FR, et al. Phase II trial of ^{131}iodine tositumomab with high-dose chemotherapy and autologous stem cell transplantation for relapsed diffuse large B cell lymphoma. *Biol Blood Marrow Transplant*. 2013;19:123-128.
60. Shimoni A, Avivi I, Rowe JM, et al. A randomized study comparing yttrium-90 ibritumomab tiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. *Cancer*. 2012;118:4706-4714.
61. Arne K, Laurell A, Jerkeman M, et al. Nordic MCL3 Study: Zevalin combined with high-dose chemotherapy followed by autologous stem cell support as late intensification for mantle cell lymphoma (MCL) patients <66 years not in CR after induction chemo-immunotherapy: no benefit of Zevalin. *ASH Annual Meeting Abstracts*. 2012;120:747.
62. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a non-randomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112:2687-2693.
63. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184-4190.
64. Briones J, Novelli S, Marco JAG, et al. Autologous stem cell transplantation with yttrium-90–ibritumomab tiuxetan (Zevalin) plus BEAM conditioning in patients with refractory non-Hodgkin diffuse large B-cell lymphoma: results of a prospective, multicenter, Phase II clinical trial. *ASH Annual Meeting Abstracts*. 2012;120:1978.
65. Decaudin D, Mounier N, Tilly H, et al. (90)Y-ibritumomab tiuxetan (Zevalin) combined with BEAM (Z -BEAM) conditioning regimen plus autologous stem cell transplantation in relapsed or refractory low-grade CD20-positive B-cell lymphoma: a GELA phase II prospective study. *Clin Lymphoma Myeloma Leuk*. 2011;11:212-218.
66. Zipp L, Saliba RM, Valverde R, et al. Mature results of BEAM/high-dose rituximab versus BEAM/yttrium-90 ibritumomab tiuxetan (Zevalin) and autologous stem cell transplantation (ASCT) for relapsed CD20$^+$ follicular and diffuse large B-cell lymphoma: survival outcomes and risk of secondary malignancies. *ASH Annual Meeting Abstracts*. 2011;118:2005.
67. Hamadani M. Reappraising the role of autologous transplantation for indolent B-cell lymphomas in the chemoimmunotherapy era: is it still relevant? *Bone Marrow Transplant*. 2013;19:1288-1300.
68. Hari P, Carreras J, Zhang MJ, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. *Biol Blood Marrow Transplant*. 2008;14:236-245.
69. Baron F, Maris MB, Sandmaier BM, et al. Graft-versus-tumor effects after allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning. *J Clin Oncol*. 2005;23:1993-2003.
70. Gopal AK, Guthrie KA, Rajendran J, et al. ^{90}Y-Ibritumomab tiuxetan, fludarabine, and TBI-based nonmyeloablative allogeneic transplantation conditioning for patients with persistent high-risk B-cell lymphoma. *Blood*. 2011;118:1132-1139.
71. Shimoni A, Zwas ST, Oksman Y, et al. Ibritumomab tiuxetan (Zevalin) combined with reduced-intensity conditioning and allogeneic stem-cell transplantation (SCT) in patients with chemorefractory non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2008;41:355-361.
72. Bethge WA, Lange T, Meisner C, et al. Radioimmunotherapy with yttrium-90-ibritumomab tiuxetan as part of a reduced-intensity conditioning regimen for allogeneic hematopoietic cell transplantation in patients with advanced non-Hodgkin lymphoma: results of a phase 2 study. *Blood*. 2010;116:1795-1802.
73. Khouri IF, Saliba RM, Erwin WD, et al. Nonmyeloablative allogeneic transplantation with or without ^{90}yttrium ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. *Blood*. 2012;119:6373-6378.
74. Bethge WA, von Harsdorf S, Bornhauser M, et al. Dose-escalated radioimmunotherapy as part of reduced intensity conditioning for allogeneic transplantation in patients with advanced high-grade non-Hodgkin lymphoma. *Bone Marrow Transplant*. 2012;47:1397-1402.
75. Gopal AK, Press OW, Wilbur SM, et al. Rituximab blocks binding of radiolabeled anti-CD20 antibodies (Ab) but not radiolabeled anti-CD45 Ab. *Blood*. 2008;112:830-835.
76. Pagel J, Gooley T, Rajendran J, et al. Allogeneic hematopoietic cell transplantation after conditioning with ^{131}I-anti-CD45 antibody plus fludarabine and low-dose total body irradiation for elderly patients with advanced acute myeloid leukemia or high-risk myelodysplastic syndrome. *Blood*. 2009;114:5444-5453.
77. Pagel JM, Orgun N, Hamlin DK, et al. A comparative analysis of conventional and pretargeted radioimmunotherapy of B-cell lymphomas by targeting CD20, CD22, and HLA-DR singly and in combinations. *Blood*. 2009;113:4903-4913.
78. Kanda J, Lopez RD, Rizzieri DA. Alemtuzumab for the prevention and treatment of graft-versus-host disease. *Int J Hematol*. 2011;93:586-593.
79. Waldmann H, Hale G. CAMPATH: from concept to clinic. *Philos Trans R Soc Lond B Biol Sci*. 2005;360:1707-1711.
80. Hale G, Xia MQ, Tighe HP, et al. The CAMPATH-1 antigen (CDw52). *Tissue Antigens*. 1990;35:118-127.
81. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007;25:5616-5623.
82. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002;99:3554-3561.
83. Pérez-Simón JA, Kottaridis PD, Martino R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. *Blood*. 2002;100:3121-3127.
84. Hale G, Zhang MJ, Bunjes D, et al. Improving the outcome of bone marrow transplantation by using CD52 monoclonal antibodies to prevent graft-versus-host disease and graft rejection. *Blood*. 1998;92:4581-4590.
85. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. *Blood*. 2000;96:2419-2425.
86. Chakraverty R, Peggs K, Chopra R, et al. Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen. *Blood*. 2002;99:1071-1078.
87. Delgado J, Thomson K, Russell N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. *Blood*. 2006;107:1724-1730.
88. Peggs KS, Kayani I, Edwards N, et al. Donor lymphocyte infusions modulate relapse risk in mixed chimeras and induce durable salvage in relapsed patients after T-cell–depleted allogeneic transplantation for Hodgkin's lymphoma. *J Clin Oncol*. 2011;29:971-978.
89. Peggs KS, Sureda A, Qian W, et al. Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. *Br J Haematol*. 2007;139:70-80.
90. Bross PF, Beitz J, Chen G, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. *Clin Cancer Res*. 2001;7:1490-1496.
91. Wadleigh M, Richardson PG, Zahrieh D, et al. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. *Blood*. 2003;102:1578-1582.
92. de Lima M, Champlin RE, Thall PF, et al. Phase I/II study of gemtuzumab ozogamicin added to fludarabine, melphalan and allogeneic hematopoietic stem cell transplantation for high-risk CD33-positive myeloid leukemias and myelodysplastic syndrome. *Leukemia*. 2008;22:258-264.
93. Bornhäuser M, Illmer T, Oelschlaegel U, et al. Gemtuzumab ozogamicin as part of reduced-intensity conditioning for allogeneic hematopoietic cell transplantation in patients with relapsed acute myeloid leukemia. *Clin Cancer Res*. 2008;14:5585-5593.
94. Satwani P, Bhatia M, Garvin JH, et al. A Phase I study of gemtuzumab ozogamicin (GO) in combination with busulfan and cyclophosphamide (Bu/Cy) and allogeneic stem cell transplantation in children with poor-risk CD33$^+$ AML: a new targeted immunochemotherapy myeloablative conditioning (MAC) regimen. *Biol Blood Marrow Transplant*. 2012;18:324-329.
95. Siegel AB, Goldenberg DM, Cesano A, et al. CD22-directed monoclonal antibody therapy for lymphoma. *Semin Oncol*. 2003;30:457-464.
96. Leonard JP, Goldenberg DM. Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene*. 2007;26:3704-3713.

97. Ricart AD. Antibody–drug conjugates of calicheamicin derivative: gemtuzumab ozogamicin and inotuzumab ozogamicin. *Clin Cancer Res*. 2011;17:6417-6427.
98. Kharfan-Dabaja MA, Bazarbachi A. Emerging role of CD20 blockade in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2010;16:1347-1354.
99. Arai S, Sahaf B, Narasimhan B, et al. Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. *Blood*. 2012;119:6145-6154.
100. Allen JL, Fore MS, Wooten J, et al. B cells from patients with chronic GVHD are activated and primed for survival via BAFF-mediated pathways. *Blood*. 2012;120:2529-2536.
101. van Heeckeren WJ, Vollweiler J, Fu P, et al. Randomised comparison of two B-cell purging protocols for patients with B-cell non-Hodgkin lymphoma: in vivo purging with rituximab versus ex vivo purging with CliniMACS CD34 cell enrichment device. *Br J Haematol*. 2006; 132:42-55.
102. Hanley PJ, Shaffer DR, Cruz CR, et al. Expansion of T cells targeting multiple antigens of cytomegalovirus, Epstein-Barr virus, and adenovirus to provide broad antiviral specificity after stem cell transplantation. *Cytotherapy*. 2011;13:976-986.
103. Borthakur G, Rosenblum MG, Talpaz M, et al. Phase 1 study of an anti-CD33 immunotoxin, humanized monoclonal antibody M195 conjugated to recombinant gelonin (HUM-195/rGEL), in patients with advanced myeloid malignancies. *Haematologica*. 2013;98: 217-221.
104. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012;30:4462-4469.
105. Hohloch K, Sahlmann CO, Lakhani VJ, et al. Tandem high-dose therapy in relapsed and refractory B-cell lymphoma: results of a prospective phase II trial of myeloablative chemotherapy, followed by escalated radioimmunotherapy with (131)I-anti-CD20 antibody and stem cell rescue. *Ann Hematol*. 2011;90:1307-1315.
106. Krishnan A, Nademanee A, Fung HC, et al. Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:90-95.
107. Nademanee AP, Raubitschek A, Palmer J, et al. ^{90}y-Ibritumomab tiuxetan (Zevalin) may enhance anti-lymphoma effect of reduced-intensity fludarabine and melphalan regimen in patients with relapsed, refractory B-cell non-Hodgkin lymphoma (NHL) undergoing allogeneic hematopoietic cell transplant (allo-HCT). *ASH Annual Meeting Abstracts*. 2009;114:3357.